Acute Renal failure: Pathogenesis and Management

Dr Siddique
Renal Unit
42yr old male pt Mr BB transferred from KEH with ethylene glycol overdose.
Pt transferred from KEH with hx of +/- 500ml ethylene glycol on 3/3/2006 and subsequently developed:
- Anuria for 24hr
- Abdominal cramps, no nausea, vomiting and diarrhea.
- Confusion, disorientation and no focal deficits
• PMH
  ➢ Hx of depression and Rx at ADH but not on medication.
  ➢ First suicide attempt
  ➢ DEARTH –nil

SH-
  ➢ self employed
  ➢ Significant smoking and alcohol hx
• Stable
• Apyrexial
• BP-135/65
• Pulse-90/min reg, good vol
• RR-26/min
• No urine output in 24hr
• CVP-10cmH20
• Anicteric
• Not fluid overloaded
• No asterixis
• Acidotic breathing
Chest - Clear
Cvs - No raised JVP
  ➢ Apex undisplaced
  ➢ Normal HS and no murmurs
PA – SNT
CNS - GCS (M5E4V3)
Confused
PEARL
Fundi normal
  • Reduced visual acuity ➔ light perception B/L
• No cranial nerve deficits
• Motors normal bulk, increased tone globally, increased reflexes globally and plantars up going

• Urine dipstix-nad
Investigation

FBC

- Hb-15.5  **WCC-27.15**  PLT-176

U/E

- Na-143  K-4.0  Cl-107  **CO2-9.7  AG-30.3**  **Urea-17.8**  
  **Creat -560**

LFT-

- TP-63  ALB-37  **BIL-31**  ALP-44  GGT-55  **ALT-545**
• CMP-2,26/0.65/2.34
• \textit{INR-1,52}
• 42 yr old male pt with Ethylene glycol overdose with :
  ➢ Acute renal failure
  ➢ Severe High anion gap metabolic acidosis
  ➢ Toxin-induced hepatitis
  ➢ Encephalopathy
  ➢ Blindness
ACUTE RENAL FAILURE: PATHOGENESIS AND MANAGEMENT
Definition

- No clear definition
- Reduction in GFR ---- often reversible
- Acute and sustained increase in creatinine conc. of:
  - 44.2umol/l if baseline < 221umol/l
  - Increase in creatinine more than 20% if baseline >221umol/l
Classification

- Oliguric
  
  < 400ml uo /24h

- Non-oliguric
  
  > 400ml uo /24h

- Anuric
  
  < 100ml uo /24h

Complete obstruction/bil. renal infarction/cortical necrosis/renal vein thrombosis/ATN
RIFLE Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>GFR criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Serum creatinine increased 1.5 times</td>
<td>&lt;0.5 mL kg⁻¹ h⁻¹ for 6 h</td>
</tr>
<tr>
<td>Injury</td>
<td>Serum creatinine increased 2.0 times</td>
<td>&lt;0.5 mL kg⁻¹ h⁻¹ for 12 h</td>
</tr>
<tr>
<td>Failure</td>
<td>Serum creatinine increased 3.0 times or creatinine=355 µmol/L when there was an acute rise of &gt;44 µmol/L</td>
<td>&lt;0.3 mL kg⁻¹ h⁻¹ for 24 h or anuria for 12 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent acute renal failure; complete loss of kidney function for longer than 4 weeks</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>End-stage renal disease for longer than 3 months</td>
<td></td>
</tr>
</tbody>
</table>
Epidemiology

• 172 cases per million per yr in UK with ARF(creat >500)

• 22 per million per yr receiving dialysis

• 5% -20% of critical ill pts have episodes of ARF→MOF
Causes of Acute Renal Failure

Prerenal
- Absolute decrease in effective blood volume
  - Haemorrhage
  - Volume depletion
- Relative decrease in blood volume (ineffective arterial volume)
  - Congestive heart failure
  - Decompensated liver cirrhosis
- Arterial occlusion or stenosis of renal artery
  - Haemodynamic form
    - NSAIDs
    - ACE inhibitors or angiotensin-II receptor antagonists in renal-artery stenosis or congestive heart failure

Intrinsic renal
- Vascular
  - Vasculitis, malignant hypertension
- Acute glomerulonephritis
  - Postinfectious glomerulonephritis, disease caused by antibody to glomerular basement membrane
- Acute interstitial nephritis
  - Drug-associated
- Acute tubular necrosis

Postrenal
- Obstruction of collecting system or extrarenal drainage
  - Bladder-outlet obstruction
  - Bilateral ureteral obstruction

Ischaemic

Nephrotoxic
- Exogenous
  - Antibiotics (gentamicin)
  - Radio contrast agents
  - Cisplatin
- Endogenous
  - Intratubular pigments (haemoglobinuria, myoglobinuria)
  - Intratubular proteins (myeloma)
  - Intratubular crystals (uric acid, oxalate)
Pre-Renal Failure

- Drugs that provoke ARF → NSAIDS → can reduce GFR in some situation:
  - Atherosclerotic CVD (>60 yrs)
  - Renal insufficiency (creatinine >180 umol/l)
  - States of renal hypoperfusion e.g., cirrhosis, nephrotic syndrome, CCF, diuretic use

- ACEI/ARB → 6%-23% with bilateral RAS or unilateral stenosis of solitary kidney
• Tacrolimus and cyclosporine cause vasoconstriction of small vessels.
Intrinsic Renal Causes

• Causes
  • Vessels
  • Glomerulus
  • Tubules
  • Interstitium

• Pre-renal $\leftrightarrow$ ischaemic ATN

Toxins:
  – Aminoglycosides
  – Radiocontrast agents
  – Heme pigment
  – Chemotx
• Pathogenesis of Acute Pre-renal failure -
Ischaemic ARF

- RBF is 25% CO
- Most blood to cortex
- Progressive drop in Po2 from medulla to cortex
- Borderline chronic O2 deprivation in PCT and medullary thick AL loop of Henle - high metabolic activity
• Hypovolemia → Fall in systemic blood pressure → activation of neurohumoral vasoconstrictive system

• Autoregulation of RBF and GFR under narrow limits

• Initially → vasodilators (NO and PGI2)

• Later → Angiotensin II → maintain glomerular pressure
Hypovolemia

- Activation of RAS
- Activation of AVP release
- Sympathetic system activated
• Increase in CO, cerebral and renal blood flow → GFR maintained
• Reduced BF cause afferent vasodilation due to myogenic reflexes, NO and PGI2
• Angiotensin II cause efferent arteriole vasoconstriction
• Maintainence of intraglomerular pressure, GFR and filtration fraction
• Decrease RBF by 30% to 50% ➔ selective drop BF to medulla
• Imbalance bt vasodilator and vasoconstrictors
• Autoregulatory vasodilation max at systolic pressure 80mmHg
• Autoregulation ➔ overwhelmed
• Ischaemia
• Worse in elderly, HPT nephroscerosis, diabetic nephropathy, NSAIDS
• Structural changes:
• Redistribution of Na/K APTase
• Depletion of cellular ATP → intracellular acidosis → increase in cytosolic Ca2+ → activate proteases and phospholipases → Change in polarity and integrity of tight jxn (alt of cytoskeleton) → break down in cytoskelton
• Lysosomal disruption → denature DNA and proteins
• **Reactive oxygen species:**
  – Reperfusion leads to rapid burst of oxidant formation--. Many sources $\rightarrow$ peroxidation of CM

• **Purine depletion:**
  – Ischemia leads to breakdown of ATP. Leakage out of cells and constrict intrarenal arterioles and form ROS.

• **Phospholipases:**
  – Activated, increases permeability to cell and mitochondrial membrane $\rightarrow$ affect bioenergy of cell
• Swelling of tubules and endothelium and adherence of neutrophils to venules and capillaries
• Vascular congestion
• Hypoxia \rightarrow \text{Integrins (cell to cell adhesion)} move from basolateral to apical location.

• Tubular cell desquamation

• Apoptosis \rightarrow \text{programmed cell death}
Repair of renal injury:

- Phase 1 - Cell death and exfoliation
- Phase 2 – Poorly diff. epithelial cells appear → stem cell
- Phase 3 – Increased prolif of surviving PCT cells
- Phase 4 – Regenerative tubular cells → diff. to normal prox. Tubule epithelium

Proximal tubules undergo repair

In cortex is sublethally injured and repair with reperfusion
**Glomerular and Medullary**

- Increased vasoconstriction in response to: endothelin, adenosine, angiotensin II, thromboxane $A_2$, leukotrienes, sympathetic nerve activity
- Decreased vasodilation in response to: nitric oxide, prostaglandin $E_2$, acetylcholine, bradykinin
- Increased structural damage to endothelial and vascular smooth-muscle cells
- Increased leucocyte-endothelial adhesion, vascular obstruction, leucocyte activation, and inflammation

**Decreased oxygen**

- Cytoskeletal breakdown
- Loss of cell polarity
- Apoptosis and necrosis
- Desquamation of viable and necrotic cells
- Tubular obstruction
- Backleak

**Microvascular**

**Tubular**
Nephrotoxic ARF

• Intra-renal vasoconstriction eg contrast nephropathy
  – Reduced RBF and reduced GFR
  – Acute 24hr to 48 hr and reverse in 3-5 days

• Direct tubular toxicity/intratubular obstruction
  – Aminoglycosides and cisplatin eg
    • Accumulate in PCT and reduce ATP
    • Impair solute transport
    • ROS injury
- Hb and Myoglobin
  - acidosis and hypovolemia → cast formed → toxic to tubule (intratubular cast)
  - Inhibitor of NO → vasoconstriction → ischaemia

- IgA Light chain →
  - toxic to tubule
  - Intratubular obstruction
• Post-renal ARF
  – Obstruction $\rightarrow$ cont GFR cause increase in intraluminal pressure upstream $\rightarrow$ gradual dilation of prox. ureter and calyces $\rightarrow$ arteriolar vasoconstriction and reduced GFR
Therapeutic Targets

- Offsetting vasoconstriction
  - Calcium channel blockade
  - Endothelin blockade
  - Atrial natriuretic factor
  - Adenosine receptor blockade
  - NO regulation
• Limiting inflammation
• Anti-adhesion strategies
  Anti-icam
  Anti-integrins
Biocompatible membranes (cytokine absorb)
• Altering cell outcome
• Growth factors
  Epedermal growth factors
  Insuline like growth factors
• Survival factors
  Trophic cytokines
  DNA repair enzymes
• Dialysis prescription
  High flux membranes
  CAVVHD
  CVVHD
  CVVH
Management of Acute Renal Failure

- Management priorities in patients with acute renal failure: Search for and correct prerenal and postrenal factors
- Review medications and stop administration of nephrotoxins
- Optimise cardiac output and renal blood flow
- Restore and/or increase urine flow
- Monitor fluid intake and output; measure bodyweight daily
• Search for and treat acute complications (hyperkalaemia, hyponatraemia, acidosis, hyperphosphataemia, pulmonary oedema)

• Provide early nutritional support
• Search for and aggressively treat infections

• Expert nursing care (management of catheter care and skin in general; psychological support)

• Initiate dialysis before uraemic complications emerge

• Give drugs in doses appropriate for their clearance
• **Intra-vascular overload**-
  – Dialysis → ultrafiltration
  – Salt(1-2g/d
  – Restrict fluid 1L/d
  – Diuretics

• **Hyponatremia**-
  – Restrict enteral free water or hypotonic soln

• **Hyperkalemia**

• **Metabolic acidosis**
  – Restrict prot -0.6g/kg/d
  – NaHCO3( HCO3<15mmol/l of Ph<7,2
  – Dialysis
Hyperphosphatemia
Restrict in diet (<800mg/d)

Hyperuricaemia –If <0.89mmol/l  ➔ no Rx
Nutrition:
    ➢ Prot <0.6g/kg/d
    ➢ CH0-100g/d
    ➢ Parental/enteral if pt catabolic of prolonged rx

➢ DOSE ADJUSTMENT OF DRUG
Indication for dialysis

- Oliguria: urine output <200 mL in 12 h
- Anuria: urine output <50 mL in 12 h
- Hyperkalaemia: potassium concentration >6.5 mmol/L
- Severe acidaemia: pH <7.0
- Azotaemia: urea concentration >30 mmol/L
• Uraemic encephalopathy

• Uraemic neuropathy/myopathy

• Uraemic pericarditis

• Plasma sodium abnormalities: concentration >155 mmol/L or <120 mmol/L

• Hyperthermia

• Drug overdose with dialysable toxin
Intermittent dialysis

- Advantages:
  - Low risk of bleeding
  - More suitable for severe hyperkalemia
  - Lower cost

- Disadvantages
  - Available staff
  - Diff haemodynamic control
  - Inadequate dialysis dose
  - Inadequate fluid control
  - Not suitable with intracranial HPT
Continuous dialysis

**Advantages**
- Better haemodynamic control
- Fewer arrhythmias
- Better plasma gas exchange
- Better biochemical control
- Shorter stay in ICU

**Disadvantages**
- Higher risk of bleeding
- Long term immobilisation of pt
- Filter problems (rupture, clotting)
- Greater cost
Intermittent dialysis → Daily dialysis vs alternate day dialysis.
Mortality 26% vs 46% (Schiffl et al, 2002)

Continuous → Pt undergoing CVVHD had better rates with filtration 35-45ml/kg/hr than lower rates
No comparison B/t Intermittent and Continuous
Slow continuous daily dialysis have advantages of to modalities
Prognosis

• Mortality
  – 50% and changed little in 30 yrs
  – Obstetric pts 15%
  – Toxin-related -30%
  – Trauma and major surgery -60%
  – Moderate sepsis - 19%
  – Severe sepsis - 23%
  – Septic shock- 51 %